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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,724	JACOBS ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 03/12/07 has been acknowledged.
Claims 6-28 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Double Patenting

Claims 6-11 and 17-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,682,745 for the same reasons of record as set forth in the office action mailed on 09/11/06.

Claims 6-8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,120,775 (ref. of record), for the same reasons of record as set forth in the office action mailed on 09/11/06.

Response to Arguments

Regarding the double patenting issues above, the applicant requested the rejection be held in abeyance until allowable subject matter is identified, therefore the instant rejection has been maintained.

Claim Objections

Claim 28 is objected to because of the following informalities: The instant claim depends upon claim 1, which has been canceled. Considering this a mere typographical error changing "claim 1" to -- claim 21-- has been suggested. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 21-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter). The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not tech *"A method for systemic application of live attenuated bacteria to a mammal, wherein the method comprises administering the live attenuated bacteria submucosally to the mammal, the live attenuated bacteria cause abscess and/or lesion formation in the mammal if the live attenuated bacteria are instead administered intramuscularly or intradermally to the mammal, and any abscess and/or lesion formation at the site of the submucosal administration is less in total size than the abscess and/or lesion formation that would occur if the bacteria are instead administered intramuscularly or intraderamally to the mammal*". The applicant fails to point out where in the specification there is support for the invention as claimed. At best the applicant asserts that "New claims 21 and 22 are supported by Applicants' specification at, for example, page 1, lines 22-30; page 2, lines 17-28; and Examples 1-3 on pages 7-9. A careful review by the examiner of the specification failed to identify any support for this new limitation. Therefore the invention as claimed is not supported by the specification as filed. As MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph -

written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." So claims 1 and 41-75 are apparently new matter. No pages or place in the specification was cited to support this amendment. Since no basis has been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

Claims 6-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of the instant invention as claimed encompasses a method of administering a live attenuated bacterial vaccine (any bacteria) to a mammal by injecting the vaccine into submucosal layer of a mammal. The scope of invention as claimed further encompasses a method for reducing the amount of adverse reaction in a mammal at injection site of live attenuated bacterial vaccine (any bacteria) by administering the vaccine submucosally. In addition the scope of invention as claimed encompasses a method for systemic application of live attenuated bacteria to a mammal wherein the live attenuated bacteria is administered submucosally.

The scope of invention as claimed encompasses the use of any and all live attenuated bacteria. At best the instant specification only discloses the use of *Streptococcus equi* attenuated strains (TW 928 and TW928/sls), which are deletion mutant vaccine strains (spec. page 7, example-1). Besides TW 928 (*Streptococcus equi)* the instant specification fails to disclose any live attenuated vaccine obtained from any other bacterial strain. Especially the specification fails to disclose a live attenuated vaccine obtained from *Actinobacillus equili, A. pleuropneumoniae; Actinomyces pyoyenes, Botdetella bronchiseptica, Brucella abortus, Clostridium perfringens, Corynebacterium bovis, C pseudotuberculosis, Erysipelotrix rhusioipathiae, Escherichia coli, Haemophilus parasuis, Leptospira canicola, L. hardjo, L icterohaemorrhagiae, L. poriona, Mycobacterium bovis,*

Mycoplasma bovis, M. hyopneumoniae, Noccatdia asteroides, Pasteurella haemolytica, P. multocida, Pseudomonas mallei, Rhodococcus equi, Salmonella cholerasuis, S. dublin, S. typimurium, Serpulina hyodysenteriae, Staphylococcus aureus, Streptococcus agalactiae, St. pneumoniae, St.suis, or St. uberis explicitly or implicitly as putatively considered by the applicant.

The state of the art regarding attenuated bacterial vaccine was such that a rational approach to design a live attenuated bacterial vaccine involves genetic modification of the bacterial pathogen to make the pathogen less virulent while maintaining the stability of protective antigen expression that provides immune protection. The attenuation should be an inherent property of the bacterial vaccine and not be dependent on fully functional host defenses and immune response capabilities. (Curtiss R. J. Clin. Invest. 110(8):1061-1066, 2002, *ref of record*). In addition, the attenuation of a bacterium requires the modification of specific bacterial genes that render the bacterial strain non-virulent. For example, inactivation of PhoP/phoq regulatory system in S. typhi results in strains, which are suitably attenuated for use as vaccines (Tiball et al Vaccine 19:4175-4184, 20001, *ref of record*, see page 4177 sec 3.1). Even though instant specification discloses only *Streptococcus equi* based attenuated strains (TW 928 and TW928/sls) the disclosure is considered insufficient, since the specification fails to disclose how to attenuate of any other species of bacteria that can be used as a vaccine without any adverse reaction. The state of the art clearly teaches that understanding of regulatory pathways that affect bacterial virulence and protective antigens that provides long-term immune protection are consider germane to the development of a live attenuated bacterial vaccine.

Furthermore, the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206,*

18 USPQ2d 1016, 1021 (Fed. Cir. 1991). In the instant case claims to live attenuated bacteria has been defined only by a statement of bacterial growth and proliferation (live attenuated) which conveyed no distinguishing information about the identity of various live attenuated bacterial species (as claimed), such as genetic modification or antigenic characteristics.

In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described. Besides TW 928 (*Streptococcus equi)* the specification does not describe any other live attenuated bacteria as listed above. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In instant case live attenuated *Streptococcus equi does not represent a common core structure of the genus claimed sine bacterial strains as claimed represent species that are distinct.* Since the specification fails to disclose any other live attenuated bacteria or a common relevant identifying characteristics, it is not possible to envision the claimed method in view of product that need to be administered. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). As stated above the disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. The state of the art clearly teaches that understanding of regulatory pathways that affect bacterial virulence and protective antigens that provides long-term immune protection are consider germane to the development of a live attenuated bacterial vaccine.

According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 6-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for protecting a mammal against *Streptococcus equi* infection by submucosal administration of a live attenuated *Streptococcus equi* strain (TW980), does not reasonably provide enablement for a method for protecting a mammal against all bacterial infection by administering any live bacterial vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of invention

The instant invention relates to administration of live attenuated bacterial vaccine(s).

Breadth of Claims and Guidance Provided in the Specification

The scope of the instant invention as claimed encompasses a method of administering a live attenuated bacterial vaccine (any bacteria) to a mammal by injecting the vaccine into submucosal layer of a mammal. The scope of invention as claimed further encompasses a method for reducing the amount of adverse reaction in a mammal at injection site of live attenuated bacterial vaccine (any bacteria) by administering the vaccine submucosally. In addition the scope of invention as claimed encompasses a method for systemic application of live attenuated bacteria to a mammal wherein the live attenuated bacteria is administered submucosally.

However, the instant specification only discloses the use of ***Streptococcus equi* attenuated strains** (TW 928 and TW928/sls), which are deletion mutant vaccine strains (spec. page 7, example-1). Besides TW 928 (*Streptococcus equi)* the instant specification fails to disclose any live attenuated vaccine obtained from any other bacterial strain. Especially, the specification fails to disclose a live attenuated vaccine obtained from *Actinobacillus equili, A. pleuropneumoniae, Actinomyces pyoyenes, Botdetella bronchiseptica, Brucella abortus, Clostridium perfringens, Corynebacterium bovis, C pseudotuberculosis, Erysipelotrix rhusioipathiae, Escherichia coli, Haemophilus parasuis, Leptospira canicola, L. hardjo, L icterohaemorrhagiae, L. poriona, Mycobacterium bovis, Mycoplasma bovis, M. hyopneumoniae, Noccatdia asteroides, Pasteurella haemolytica, P.*

multocida, Pseudomonas mallei, Rhodococcus equi, Salmonella cholerasuis, S. dublin, S. typimurium, Serpulina hyodysenteriae, Staphylococcus aureus, Streptococcus agalactiae, St. pneumoniae, St.suis, or St. uberis explicitly or implicitly as putatively claimed herein.

State Of Art And Predictability

The state of the art at the time of filing teaches that the development of a bacterial vaccine is considered highly unpredictable because the safety and efficacy of the vaccine is dependent upon the way the bacterial antigens are presented to the host and the sate of the host immune response it self. Further more several safety concerns of the live bacterial vaccine strain have been raised. Before using pathogenic bacteria for vaccination purposes, its pathogenicity must be weakened via attenuation. Attenuation usually involves deletion of essential virulence factors or mutation of genes encoding metabolic enzymes whose function is essential for survival outside the laboratory. Inactivation of a metabolic gene has the advantage that the bacteria still express virulence determinants important to elicit a protective immune response. Appropriate stable auxotrophic strains are usually not able to replicate in the human body and can safely be used even in immune compromised individuals. Defined deletions of at least two metabolic essential genes are usually used and decrease the probability of reversion to virulence. In general the spread of live bacterial vaccines to the environment is a concern. However, attenuated human pathogens are usually not adapted to live outside its host. (see page 6, Detmer et al, Microb Cell Fact. 23(5):1-12, 2006).

In addition the state of attenuated bacterial vaccine art teaches was such that a rational approach to design a live attenuated bacterial vaccine involves genetic modification of the bacterial pathogen to make the pathogen less virulent while maintaining the stability of protective antigen expression that provides immune protection. The attenuation should be an inherent property of the bacterial vaccine and not be dependent on fully functional host defenses and immune response capabilities. (Curtiss R. J. Clin. Invest. 110(8):1061-1066, 2002, ref. of record). In addition, the attenuation of a bacterium requires the modification of specific bacterial genes that render the bacterial strain non-virulent. For example, inactivation of PhoP/phoq

regularoty system in S. typhi results in strains, which are suitably attenuated for use as vaccines (Tiball et al Vaccine 19:4175-4184, 20001, *ref of record*, see page 4177 sec 3.1). Furthermore, the development of live attenuated bacterial vaccine has not been always predictable. For example, development of a live attenuated *Shigella* vaccine that is sufficiently attenuated to be non-reactive yet adequately invasive to be highly immunogenic took 30 years in making, since it required substantial understanding of molecular genetic basis of virulence of *Shingella* (Curtiss page 1063, col.2). The specification fails to provide any guidance regarding how to make a live attenuated bacterium selected from the above-mentioned species (see claims 7, 11, 12 and 20). The specification fails to disclose what are the bacterial regulatory systems in these bacteria, mutation of which would result in the making of a live attenuated bacterial strain that would provide protect a mammal against any specific bacterial infection. The state of the art clearly teaches that understanding of regulatory pathways that affect bacterial virulence and protective antigens that provides long-term immune protection are consider germane to the development of a live attenuated bacterial vaccine.

The USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of skill.

The disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the

public to understand and carry out the invention. In instant case to practice the invention, as claimed one would require a live attenuated vaccine on hand. However the specification fails to provide any guidance regarding how make a live attenuated vaccine for all bacterial strains (other than *Streptococcus equi* attenuated strains TW928). At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

In addition, sub mucosal injection of any live attenuated bacterial strain (virulent) as vaccine is not considered routine in the art and without sufficient guidance to a specific bacterial strain and vaccination outcome base upon the immune protection the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The amount of undue experimentation required would include sub mucosal injection of any live attenuated bacterial strains (as claimed) and evaluation of vaccine efficacy in order to provide immune protection. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Response to arguments

The applicant argues that invention as claimed do not specifically recite administration of a vaccine per se. Instead, it recite submucosal administration of live attenuated bacteria wherein any abscess and/or lesion formation at the site of the submucosal administration is less in total size than the abscess and/or lesion formation that would occur if the bacteria were instead administered intramuscularly or intradermally. The applicant concluded that invention as claimed do not require any specific enablement as to preparing a vaccine per se

However, applicant's arguments are found not persuasive. A vaccine is an antigenic preparation used to produce active immunity to a disease, in order to prevent or ameliorate the effects of infection by any natural or "wild" strain of the organism (definition http://en.wikipedia.org/wiki/Vaccine). The scope of invention as claimed encompasses the use of any "live attenuated bacterial vaccine". The applicant fails to establish that they are in the possession of the product to be used (entire genus) in the method as claimed (see Written Description rejection). Furthermore, considering the unpredictability in the bacterial vaccine art, the specification as filed fails to provide any guidance regarding how to make the product to be used (genus as claimed) in the methods as claimed (see Enablement rejection). The applicant fails to consider the state of the attenuated bacterial vaccine art (supra) that clearly teaches that a rational approach to design a live attenuated bacterial vaccine involves genetic modification of the bacterial pathogen to make the pathogen less virulent while maintaining the stability of protective antigen expression that provides immune protection. In addition, the attenuation of a bacterium requires the modification of specific bacterial genes that render the bacterial strain non-virulent. Since the sub mucosal injection of any live attenuated bacterial strain as vaccine is not considered routine in the art and without sufficient guidance to a specific bacterial strain and vaccination outcome base upon the immune protection the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites claim limitation *"A method for systemic application of live attenuated bacteria to mammal by administering the live attenuated bacteria submucossaly to the mammal"*. It is unclear how the systemic application is achieved when the product is applied locally i.e. submucosally. Furthermore any local administration like intramuscular, intradermal and submucosal is not considered systemic because contents delivered stays at the site of injection.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SUMESH KAUSHAL
PRIMARY EXAMINER